Naval Medical Research Institute

Bethesda, MD 20889-5607

NMRI 93-13 March 1993

AD-A264 291

LOCAL AND SYSTEMIC ABSORPTION OF PARENTERAL AND PERITONEAL ADMINISTRATION OF CEFTRIAXONE IN RATS

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TECHNICAL REVIEW AND APPROVAL
NMRI 93-13

The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for Public Release; distribution is unlimited.
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) NMRI 93-13	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Naval Medical Research Inst. — 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION Bureau of Medicine and Surgery
6c. ADDRESS (City, State, and ZIP Code) 8901 Wisconsin Avenue Bethesda, Maryland 20889-5607	7b. ADDRESS (City, State, and ZIP Code) Department of the Navy Washington, DC 20372-5120
8a. NAME OF FUNDING / SPONSORING Naval Medical Research and Development Command — 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) 8901 Wisconsin Avenue Bethesda, Maryland 20889-5605	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 63706N — PROJECT NO. M0095 — TASK NO. 001 — WORK UNIT ACCESSION NO. 1005
11. TITLE (Include Security Classification) Local and systemic absorption of parenteral and peritoneal administration of ceftriaxone in rats.	
12. PERSONAL AUTHOR(S) * PW Perdue, L Kurlansik, LD Mell, DP Gallus, JJ Nevola, KK Kazarian	
13a. TYPE OF REPORT TECHNICAL REPORT — 13b. TIME COVERED FROM 10/91 TO 10/92 — 14. DATE OF REPORT (Year, Month, Day) 93/3/3 — 15. PAGE COUNT 13	
16. SUPPLEMENTARY NOTATION * LT PW Perdue, National Naval Medical Center, Dept. of General Surgery, 8901 Wisconsin Ave., Bethesda, MD 20889-5600	
17. COSATI CODES FIELD / GROUP / SUB-GROUP	18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number) antibiotic, endotoxin, peritoneal, absorption

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

High performance liquid chromatography was used to determine plasma and peritoneal fluid ceftriaxone levels after both parenteral administration and peritoneal irrigation with ceftriaxone. Ceftriaxone in amounts greater than the minimum inhibitory concentration effective against E. coli was detected in plasma of rats that received peritoneal irrigation with 1000 mg/l ceftriaxone solution; there was no ceftriaxone present in plasma of rats that received peritoneal irrigation with 10 mg/l ceftriaxone solution. Lastly, ceftriaxone irrigation was not associated with any increase in the incidence of intraabdominal adhesions in this rat model.

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Regina E. Hunt, Command Editor	22b. TELEPHONE (Include Area Code) (301) 295-0198 — 22c. OFFICE SYMBOL MRL/RSP/NMRI

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

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ACKNOWLEDGEMENTS

This work was supported by the Naval Medical Research and Development Command, Work Unit Number 63706N M0095.001-1005. The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official at large. The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," National Research Council, DHHS, Pub. No. (NIH) 86-23 (1985). The technical assistance of HM2 A. Wakefield, HM2 B. Hendricks, HM2 J. Kelly, HM3 M. Pierce, and A. Holly is gratefully acknowledged. The editorial assistance of Mr. Edd Olds is also appreciated.

INTRODUCTION

Peritonitis is a frequent cause of sepsis and septic shock, especially in patients who receive penetrating abdominal trauma. Treatment of peritonitis includes prompt administration of systemic antibiotics effective against enteric organisms, physical removal of fecal and bacterial material from the peritoneum, and surgical restoration of gastrointestinal tract integrity. Although antibiotics are vital to the treatment of peritonitis, there may be some adverse effects to their use (1,2).

Ceftriaxone is a third-generation cephalosporin with a broad spectrum of activity against gram negative and gram positive bacteria and is eliminated from the body via renal and hepatic mechanisms (3). Ceftriaxone is administered parenterally, by either intramuscular injection or intravenous infusion. In solution, it may also be used to irrigate wounds or contaminated body cavities. The purpose of this study was to determine absorption and clearance of ceftriaxone in rats after intramuscular injection and peritoneal irrigation as well as document any increase in incidence of peritoneal adhesions after peritoneal irrigation with ceftriaxone solution.

METHODS

Male Sprague-Dawley rats (n=41) were obtained and housed in a light and temperature-controlled environment for at least one week before experimental use. Rats were randomized to receive either intramuscular injection of 30 mg/kg ceftriaxone (100mg/cc) (n=10), peritoneal lavage with 30 cc of 1000 mg/l ceftriaxone solution (n=13), or peritoneal lavage with 30 cc of 10 mg/l ceftriaxone solution (n=18). Under isoflurane inhalation anesthesia, those rats randomized to receive intramuscular injection received direct injection into the muscles of the anterior thigh. Those animals randomized to receive peritoneal lavage received a midline incision and subsequent lavage with 30 cc of 1000 mg/l or 10 mg/l solution. In each animal, the lavage solution was injected and withdrawn with an 18 gauge catheter. Lavage solution remaining in the abdomen was removed with sponges until the abdomen was relatively dry. Total contact time between the antibiotic solution and the peritoneum was approximately 2 minutes. Each incision was closed with surgical staples and rats returned to their cages. Then 0.1 cc of blood was obtained from each rat by subxiphoid cardiac puncture, under isoflurane or intramuscular ketamine anesthesia, at 1,2,4, and 6 hours in a subgroup (n=7) of those rats that received parenteral injection and at 5, 10, 20, and 60 minutes in subgroups of those rats that received peritoneal lavage with 10 mg/l solution (n=8) or 1000 mg/l solution (n=3). Peritoneal fluid was collected at laparotomy under isoflurane anesthesia in 3 of the rats that received intramuscular injection. All blood and peritoneal fluid

samples were collected in sterile heparinized tubes and centrifuged to obtain plasma. Each sample was then assayed with high performance liquid chromatography (HPLC) according to the method described by Trautmann and Haefelfinger, to determine the amount of ceftriaxone present in each sample (4). Each rat was euthanized with either carbon dioxide or isoflurane inhalation at the conclusion of the experiment.

The remaining rats received peritoneal lavage with 30 cc of 10 mg/l (n=10) or 1000 mg/l (n=10) ceftriaxone solution, were observed a total of 10 days, euthanized, and necropsied. At necropsy, the presence or absence of intraabdominal adhesions was noted and tissue from the liver, small bowel, and anterior abdominal wall preserved for histologic study.

Finally, determination of ceftriaxone susceptibility was performed by broth dilution technique. Serial twofold dilution of freshly prepared ceftriaxone was done in Brain Heart Infusion broth (BHI) (Difco, Detroit, MI), then inoculated with Escherichia coli strain B7 at approximately 10^4 bacteria/ml. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of ceftriaxone which completely prevented visible growth after 18 hours of incubation under aerobic conditions at 37°C. Two determinations of MIC were made in this fashion.

RESULTS

Mean plasma ceftriaxone levels +/- standard error after parenteral injection of 30 mg/kg are depicted in Figure 1. The mean peritoneal fluid ceftriaxone level at 2 h was 42 +/- 8 mcg/l. Mean plasma ceftriaxone levels +/- standard error after peritoneal irrigation with 30 cc of 1000 mg/l ceftriaxone solution are depicted in Figure 2. There was no detectable plasma ceftriaxone in any rat that received peritoneal irrigation with 10 mg/l ceftriaxone solution.

No gross adhesions were noted in rats that received peritoneal irrigation with dilute (10 mg/l) or concentrated (1000 mg/l) ceftriaxone solution. Histologically, there was no evidence of serositis or capsulitis in either group.

Minimum inhibitory concentration of ceftriaxone was determined to be 1.56 mg/l (mcg/ml) in two separate determinations.

DISCUSSION

Antibiotics are vital to the treatment of peritonitis and penetrating abdominal trauma. Antibiotics, while beneficial in decreasing bacterial contamination, may have adverse effects on peritoneal defense mechanisms. Cephalosporins as well as other antibiotics, in high concentrations, have been shown to decrease neutrophil chemotaxis and increase the incidence of intraabdominal adhesions after peritoneal administration (1,2). Ceftriaxone is a third generation cephalosporin with a broad spectrum against Gram-positive and Gram-negative bacteria. It has a significantly longer

half life in humans (7.3 h) that allows it to be administered to patients only once or twice a day (3). The half life in rats is much shorter, only 29 minutes (5). As a preliminary study, we wanted to insure sufficient ceftriaxone to be present in the plasma and peritoneal fluid of study rats for at least 2 h, so we determined plasma and peritoneal fluid concentrations of ceftriaxone 2 h after parenteral administration. Ceftriaxone was present in concentrations greater than the minimum inhibitory concentration (MIC) against E. coli strain B7 (1.56 mg/l) and 90% of all E. coli strains (>0.01-0.5 mg/l) in both plasma and peritoneal fluid at 2 h and in plasma until 4 h after injection. A second objective of this preliminary study was to determine if ceftriaxone was absorbed from the peritoneum after peritoneal irrigation with dilute or concentrated ceftriaxone solutions. A dilute ceftriaxone solution was chosen to minimize inhibition of peritoneal defensive cells and to provide only local antibiotic activity to the peritoneum. There was significant absorption of concentrated ceftriaxone solution (1000 mg/l) as evidenced by serum levels greater than the MIC for E. coli up to 1 h after irrigation. Conversely, there was no detectable absorption of dilute (10 mg/l) ceftriaxone irrigation. Irrigation with a concentrated antibiotic solution provides local antibiotic activity and systemic antibiotic activity through peritoneal absorption.

Numerous antibiotics, including cephalosporins, can produce adhesions after peritoneal administration (2). Tetracycline, a broad spectrum antibiotic of fungal origin, is commonly used to

completely obliterate the pleural cavity in patients after recurrent pneumothorax. Therefore, the third objective of this preliminary study was to determine if peritoneal irrigation with dilute or concentrated ceftriaxone solution did increase the incidence of intraabdominal adhesions. There were no gross or histologic effects noted after irrigation with dilute (10 mg/l) or concentrated (1000 mg/l) ceftriaxone solution in this study.

CONCLUSION

High performance liquid chromatography was used to determine plasma and peritoneal fluid ceftriaxone levels after both parenteral administration and peritoneal irrigation with ceftriaxone. Ceftriaxone in amounts greater than the minimum inhibitory concentration effective against E. coli was detected in plasma of rats that received peritoneal irrigation with 1000 mg/l ceftriaxone solution; there was no ceftriaxone present in plasma of rats that received peritoneal irrigation with 10 mg/l ceftriaxone solution. Lastly, ceftriaxone irrigation was not associated with any increase in the incidence of intraabdominal adhesions in this rat model.

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Mean Plasma Ceftriaxone
(30 mg/kg intramuscular injection)

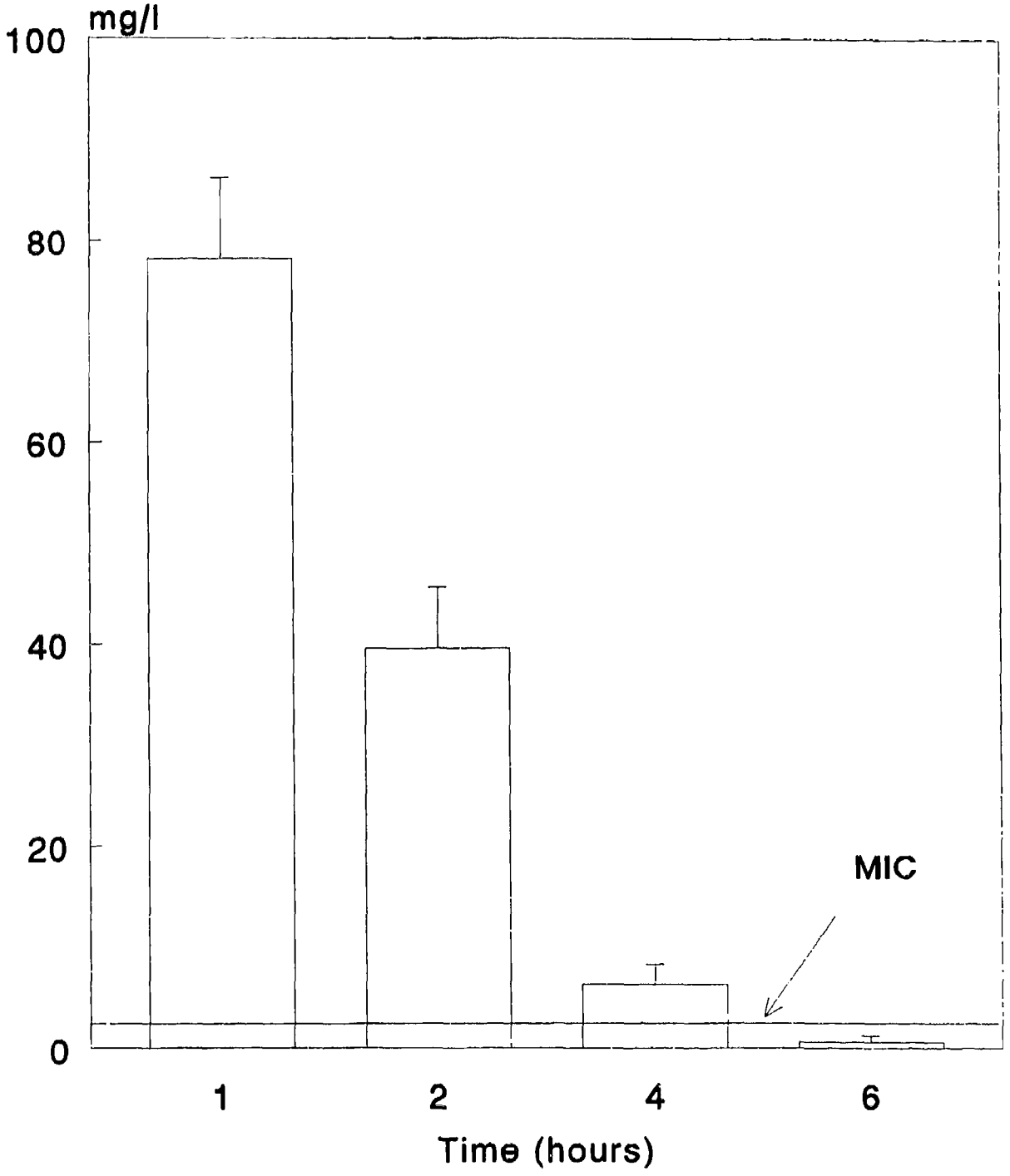

Figure 1.

Mean Plasma Ceftriaxone
(30 cc irrigation, 1000 mg/l)

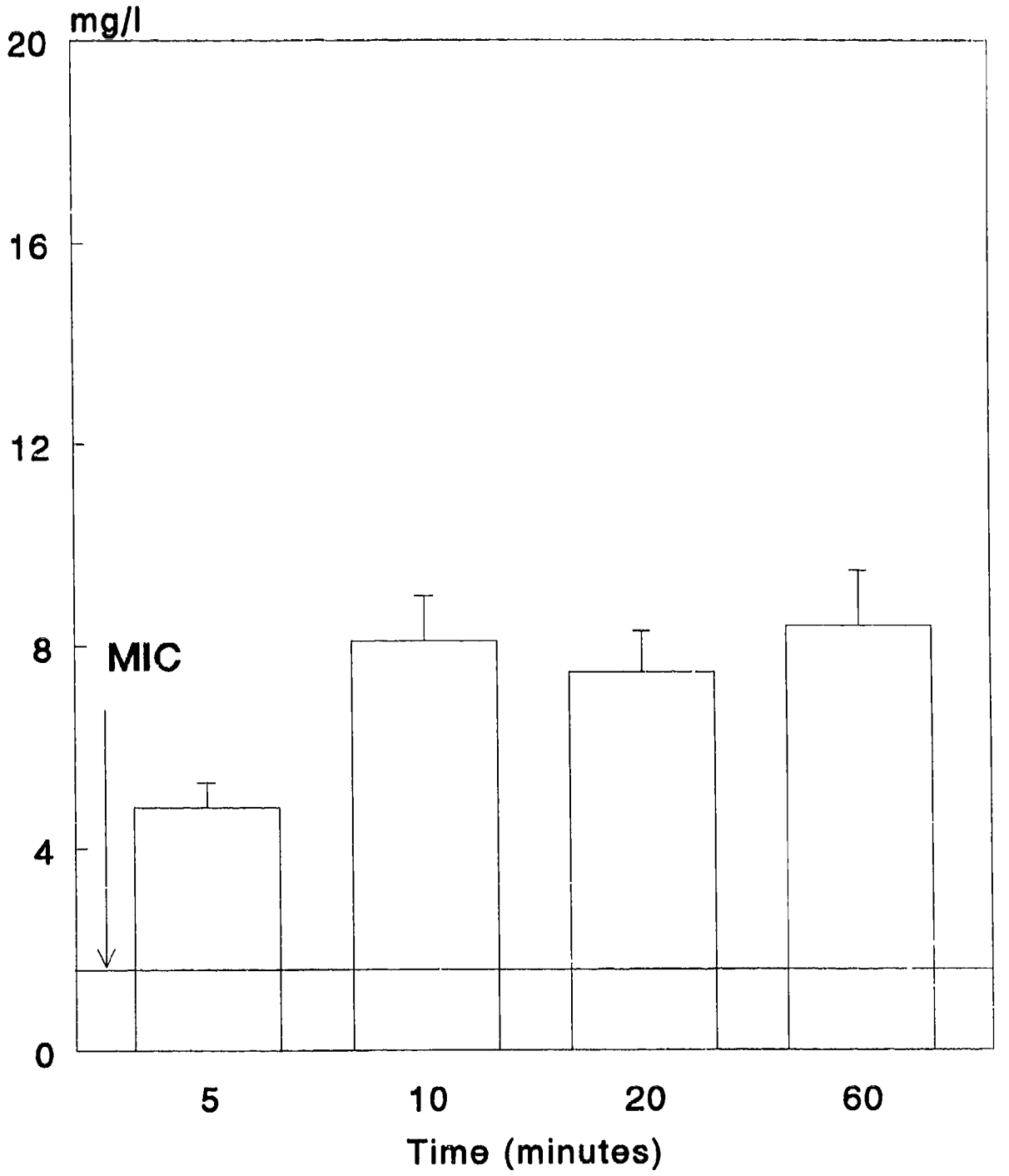

Figure 2.